ARYLATION OF MONOTHIOBARBITURIC ACID WITH ARENEDIAZONIUM SALTS

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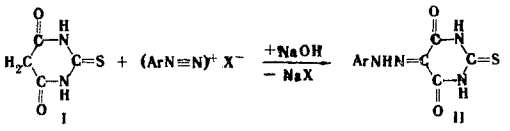
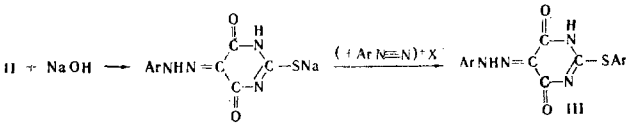
The first product under the conditions of O,S-arylation of monothiobarbituric acid is 5-arylhydrazonomonothiobarbituric acid. S-arylation then occurs to form the S-aryl ester of 5-arylhydrazonomonothiobarbituric acid. Further arylation leads to the O,S-diaryl esters of 5-arylhydrazonomonothiobarbituric acid. These esters are hydrolyzed under the influence of acids, alkalis, or hydrazine hydrate to thiophenols and phenols.

We have previously shown [1] that substances that are capable of thioamide–imidothiol tautomerism can be arylated with benzenediazonium salts at the sulfur atom and that the corresponding carboxylic acid amides can be arylated at the oxygen atom [2,3]. In aliphatic compounds [2] [RC(=O)CH_2C(=S)NHR] in which the thioamide group is separated by a methylene group from the carbonyl group, the methylene group first reacts with the benzenediazonium salt to form the corresponding arylhydrazone. The next step is S-arylation. The carbonyl group does not enter into the reaction because of the formation of an arylhydrazone and the impossibility of enolization. It seemed of interest to determine the sequence of the reaction of the benzenediazomium cation with three or more of the enumerated groupings closed into a cyclic compound. We studied this in the case of the reaction of benzenediazonium salts with monothiobarbituric acid (I).

It was established that under the conditions of O,S-arylation, as under the usual conditions [5], the active methylene group reacts first with the arenediazonium cation to form 5-arylhydrazones of monothiobarbituric acid (II). The yields of the latter are almost quantitative (Table 1). Their structures were proved by the preparation of the known hydrazone II (Ar = C_6H_5).



As in aliphatic compounds that contain thioamide and amide groups, the thioamide group proved to be more reactive in O,S-arylation. This is proved by the fact that arylhydrazones II form S-aryl esters of 5-arylhydrazonomonothiobarbituric acid (III, Table 2) with a second arenediazonium molecule:



The structures of esters III were confirmed by their alkaline and acidic hydrolysis. A thiophenol (ArSH) and an arylhydrazone of barbituric acid (IV), also obtained by alternative synthesis from barbituric acid and the arenediazonium salt, were isolated as a result of hydrolysis.

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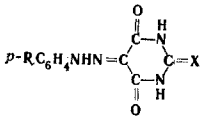
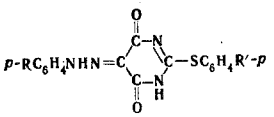
TABLE 1.



R	X	mp, °C		Empirical formula	Yield, %
		found	acc. to [5]		
H	S	>300	240	$C_{10}H_8N_4O_2S$	90
Cl	S	>240	240	$C_{10}H_7ClN_4O_2S$	80
NO_2	S	>300	240	$C_{10}H_7N_5O_6S$	90
CH_3	S	>300	240	$C_{11}H_{10}N_4O_2S$	88
SO_3Na	S	>300	[a]	$C_{10}H_7NaN_4O_5S$	90
H	O	286	284[5]	$C_{10}H_8N_4O_3$	83
Cl	O	>300	[b]	$C_{10}H_7ClN_4O_3$	87

[a] Found %: N 15.8, 15.8. Calculated %: N 16.0.
[b] Found %: N 20.8, 20.6. Calculated %: N 21.0.

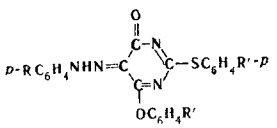
TABLE 2.



No.	R	R′	mp, °C	Empirical formula	N found, %	N calc., %	Yield, %
1	H	CH_3	116—117[a]	$C_{17}H_{14}N_4O_2S$	15,9; 16,1	16,6	8
2	H	CH_3O	114—115[a]	$C_{17}H_{14}N_4O_3S$	16,9; 17,0	16,8	8
3	H	Cl	200—201[6]	$C_{16}H_{12}ClN_4O_2S$	16,0; 16,0	15,6	14
4	NO_2	H	210[6]	$C_{16}H_{11}N_5O_4S$	19,3; 19,3	19,0	9
5	CH_3	CH_3	232[6]	$C_{18}H_{16}N_4O_2S$	15,8; 16,0	15,9	30

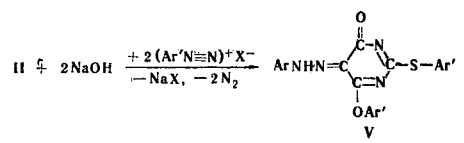
[a] From benzene.
[b] From ethanol.

TABLE 3.



No.	R	R′	mp, °C	Empirical formula	N found, %	N calc., %	Yield, %
6	H	CH_3	95—96	$C_{24}H_{20}N_4O_2S$	13,1; 13,2	13,1	6
7	H	CH_3O	61—62	$C_{24}H_{20}N_4O_4S$	12,7; 12,5	12,2	5
8	H	C_2H_5O	78	$C_{26}H_{24}N_4O_4S$	11,1; 11,1	11,5	24
9	H	NO_2	131—132	$C_{22}H_{14}N_6O_6S$	17,6; 17,7	17,1	10
10	H	Br	107—108	$C_{22}H_{14}Br_2N_4O_2S$	10,0; 10,0	10,0	14
11	H	Cl	78—79	$C_{22}H_{14}Cl_2N_4O_2S$	12,4; 12,4	11,9	16
12	H	C_2H_5OCO	84—85	$C_{28}H_{24}N_4O_6S$	10,4; 10,4	10,3	7
13	NO_2	Cl	167 (dec.)	$C_{22}H_{13}Cl_2N_5O_4S$	13,5; 13,3	13,6	11

When two molecules of alkali and two molecules of arenediazonium salt are introduced into the reaction of arylhydrazones II, one of the amide groups of the arylhydrazonomonothiobarbituric acid is O-arylated to form O,S-diaryl esters of 5-arylhydrazonomonothiobarbituric acid (2-arylthio-5-arylhydrazono-6-aryloxy-1,3-diazin-4-ones) (V, Table 3):



A phenol, a thiophenol, and an arylhydrazone of barbituric acid (IV) were obtained from the latter as a result of alkaline or acid hydrolysis.

The arylation of arylhydrazones II at the sulfur and oxygen atoms increases the solubilities of the reaction products in the same organic solvent. This made it possible to separate the reaction products by both repeated extractions and by the use of chromatography on aluminum oxide.

It should be noted that a further increase in the amount of arenediazonium salt introduced into the reaction with the sodium salt of 5-arylhydrazonomonothiobarbituric acid (II) did not result in arylation at the oxygen atom of the second amide group of this acid. This indicates that O-arylation does not occur if the amide group in the compound is not capable of amino–imidole tautomerism; this also occurred in the case of the exhaustive O,S-arylation of arylhydrazone II with arenediazonium salts. The stepwise formation of first the S-ester III and then the O,S-diester V led to the fact that an imide group that was incapable of tautomeric transformations was formed in the latter (instead of an amido group) in the 2,4 position of the diazine ring of III.

The hydrazinolysis of esters III and IV in excess hydrazine hydrate with heating gave thiophenols (ArSH).

EXPERIMENTAL

5-Arylhydrazonomonothiobarbituric Acid (II). Thiobarbituric acid (0.014 mole) was dissolved in 25 ml of 1% sodium hydroxide, and 25 ml of water and 50 ml of acetone were added. After 1 h, 6 g of sodium acetate was sprinkled into the solution, and the mass was cooled to 0°. A solution of an arenediazonium salt (from 0.014 mole of arylamine, 2-3 ml of water, 4 ml of concentrated hydrochloric acid, and 0.88 g of sodium nitrite in 3 ml of water and 5 g of ice; the diazotization time was 1 h) was then added slowly to it with stirring. An acetone-insoluble precipitate began to form immediately. After 12 h the precipitate was removed by filtration, washed with 100 ml of distilled water, and air dried. It was then reprecipitated by the addition of hydrochloric acid to a solution in 10% sodium hydroxide (100 ml) and recrystallized from ethanol.

The p-sulfophenylhydrazone was recrystallized from 30 ml of 40% alcohol.

The 5-arylhydrazonomonothiobarbituric acids (Table 1) were yellow crystalline substances that were soluble in alcohol, pyridine, dioxane, and alkalis, slightly soluble in acetone, and insoluble in benzene and ether.

5-(p-Chlorophenylhydrazono)barbituric (IVa) and 5-phenylhydrazonobarbituric acid (IVb) were similarly obtained, but barbituric acid was introduced in place of thiobarbituric acid in the reaction with the arenediazonium chloride.

Arylhydrazonobarbituric acids IVa,b were also obtained as a result of hydrolysis of the aryl esters of these acids (III and V, see below).

S-Aryl Esters of 5-Arylhydrazonomonothiobarbituric Acid (1H-2-Arylthio-5-arylhydrazono-1,3-diazine-4,6-diones) (III, Nos. 3-5, Table 2). Sodium hydroxide (0.002 mole) in 2 ml of water was added to a solution of 0.002 mole of 5-phenylhydrazonomonothiobarbituric acid in 400 ml of acetone, and 100 ml of water was then added to dissolve the precipitate. After 2 h, 0.17 g of sodium acetate was added to the solution. The mixture was cooled to 0°, and a solution of arenediazonium salt (from 0.002 mole of arylamine, 0.5 ml of concentrated hydrochloric acid, 0.13 g of sodium nitrite in 2 ml of water and 5 g of ice; the diazotization time was 1 h) was added with stirring. After 12 h the acetone was vacuum evaporated. The precipitate was removed by filtration, washed with 10 ml of distilled water, dried at room temperature, and dissolved in 5 ml of ethanol. The solution was filtered, and the filtrate was evaporated to dryness. The operation was repeated three times.

The S-(p-tolyl) ester of 5-phenylhydrazonomonothiobarbituric acid (No. 1, Table 2), the S-(p-methoxyphenyl) ester of 5-(p-methoxyphenyl)hydrazonomonothiobarbituric acid (No. 2, Table 2), the O,S-di(p-tolyl) ester of 5-phenylhydrazonomonothiobarbituric acid (No. 6, Table 3), and the O,S-di-(p-methoxyphenyl) ester of 5-phenylhydrazonomonothiobarbituric acid (No. 7, Table 3) were similarly obtained. After evaporation of the acetone, the oil was collected and dissolved in 30-50 ml of benzene. The solution was filtered to remove the solid, and the filtrate was chromatographed on aluminum oxide (layer height 6 cm, column diameter 1 cm). The first (upper) and second zones were cut out, and the reaction products were extracted from

them with 30-40 ml of acetone. Esters Nos. 1 and 2 were obtained from the first zone, and diesters Nos. 6 and 7 were obtained from the second zone.

Esters III (Table 2) are red or light-brown, crystalline substances that are soluble in acetone, benzene, alcohol, ethanol, and dioxane and insoluble in water. Their solubilities are lower than the solubilities of O,S-diaryl esters V but much higher than those of 5-arylhydrazonomonothiobarbituric acid (II).

O,S-Diaryl Esters of 5-Arylhydrazonomonothiobarbituric Acid (V, Nos. 8-13, Table 3). The arylhydrazonomonothiobarbituric acid (0.005 mole) was dissolved in 30 ml of 1% sodium hydroxide, and 400 ml of 50% aqueous acetone was added. After 1 h, the solution was cooled to 0°, 1.8 g of sodium acetate was added, and a solution of an arenediazonium salt (from 0.02 mole of arylamine, 4 ml of concentrated hydrochloric acid, and 0.7 g of sodium nitrite in 5 ml of water and 10 g of ice; the diazotization time was 1 h). After 18 h, the precipitate was removed by filtration, washed with 50 ml of distilled water, dried, ground thoroughly, and mixed with 50 ml of acetone. After 30 min, the solution was filtered to remove the insoluble material, and the filtrate was evaporated to dryness. The residue after evaporation of the acetone was treated in the same fashion two more times and dried at room temperature.

The synthesized diesters (V, Table 3) are brown or dark-brown crystalline substances. They are quite soluble in acetone, dioxane, benzene, alcohol and insoluble in water.

Alkaline Hydrolysis of the S-(p-Chlorophenyl) Ester of 5-Phenylhydrazonomonothiobarbituric Acid. Sodium hydroxide (0.04 g) was dissolved in 5 ml of ethanol, 0.18 g of the S-(p-chlorophenyl) ester of 5-phenylhydrazonomonothiobarbituric acid was added, and the mixture was refluxed on a water bath for 2 h. The mass was cooled and filtered to remove the insoluble material. The filtrate was acidified, and a double volume (with respect to the volume of the reaction mass) of water was added. p-Chlorothiophenol began to precipitate immediately. It was removed by filtration and dried to give 30% of a product with mp 51° (mp 53-54° [7]) that gave a qualitative reaction for a thiophenol. After 40 min, 33% of phenylhydrazonobarbituric acid (IVb) with mp 286° (mp 284° [6]) precipitated from the mother liquor. The products did not depress the melting points of authentic samples.

Acid Hydrolysis of the O,S-Di-(p-bromophenyl) Ester of 5-Phenylhydrazonomonothiobarbituric Acid. A 0.5 g sample of the O,S-di-(p-bromophenyl ester of 5-phenylhydrazonomonothiobarbituric acid was added to a solution of 0.2 ml of concentrated hydrochloric acid in 10 ml of ethanol, and the mixture was refluxed on a water bath for 3 h. Cooling precipitated 50% of phenylhydrazonobarbituric acid (IVb) with mp 286° (from ethanol). This product did not depress the melting point of an authentic sample.

The alcohol mother liquor was doubly diluted with water and extracted with diethyl ether. The ether was evaporated to give an oily residue with a sharp thiophenol odor that gave a qualitative reaction for thiophenol [8] and phenol [9]. To remove the phenol, the mass was allowed to stand in the air for oxidation to the disulfide until the odor of thiophenol vanished; the p-bromophenol was then extracted from it with dilute alkali, and was isolated by acidification with hydrochloric acid and determined by qualitative reactions for phenols [10]. The alkali-insoluble disulfide was dissolved in acetic acid, hydrochloric acid was added, and the disulfide was reduced with zinc dust. A grain of sodium nitrite was added, and the color change indicated the presence of a thiophenol [8].

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